

REMARKS

The present Response is filed in order to correct the inadvertent omission of Claim 6 in the listing of Claims filed in the Responses filed in September, 2003. In order to ensure that the Response is entered into the record of the present case, the arguments provided below are the same as those submitted on September 8, 2003.

As of the date of the present Office Action, Claims 2, 5, 7, 14, 29-34, 39, and 41 were pending. Applicants appreciate the Examiner's removal of his previous rejections. The remaining two rejections are discussed in the following order:

- 1) Claims 2, 5, 7 14, 29-34 and 39 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement and/or containing new matter; and
- 2) Claim 41 stands rejected under 35 U.S.C. §102(a) a allegedly being anticipated by Estell (WO 99/53078).

1) The Claims Meet the Written Description Requirement

The Examiner has rejected Claims 2, 5, 7 14, 29-34 and 39 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement and/or containing new matter. In particular, the Examiner argues that Applicants cannot exclude what was not specifically recited. Applicants have amended independent Claim 2, to remove the recitation excluding streptokinase. In case the Examiner is considering re-citing Carr (WO 98/52976) as teaching the modification of a kinase, Applicants respectfully submit that streptokinase is NOT a kinase. Although Applicants previously amended Claim 2 to recite that the kinase is not streptokinase, Applicants' representative did not intend to admit that streptokinase is actually a kinase. Indeed, upon additional research, Applicants' representative determined that this characterization is incorrect, as "streptokinase" is merely the name of a protein produced by members of the genus *Streptococcus*; it is not a "kinase," nor even an enzyme. Applicants submit that any previous implication that streptokinase is a kinase was in error and was not intended to deceive.

As known in the art, a "kinase" is an enzyme that acts by phosphorylating proteins (See e.g., Lehninger, Principles of Biochemistry, Worth Publishers, Inc., New York, NY [1982], at page 974; attached hereto at Tab 1; and Sharp (ed), Penguin Dictionary of Chemistry, The, 2nd

ed., Penguin Books, London, England [1990], at page 230; attached hereto at Tab 2). Streptokinase is NOT a kinase, as its function is to activate plasminogen by binding to it. Thus, rather than phosphorylating a protein, streptokinase binds to one (See e.g., Master Drug List--Pharmacology 2001-2002, at page 10; this document is located at ><http://www.viriniadocs.com/Master%20Drug%20List-%20Pharmacology%202001-2002.doc>; and is attached hereto at Tab 3). As indicated at Tab 3, streptokinase is "[n]ot a kinase or an enzyme, binds to pla[s]minogen to form plasmin" Furthermore, as indicated on page 2 of the printout from a web publication by Lizbeth Hedstrom (attached hereto at Tab 4), "[s]treptokinase is a plasminogen activator Unlike typical plasminogen activators, streptokinase is not a protease (nor is it a 'kinase')."

Thus, as streptokinase, which is taught by the Carr reference is NOT a kinase, the Carr reference does NOT teach nor suggest the presently claimed kinase variant having reduced allergenicity. Therefore, Applicants respectfully submit that the Claims are allowable over the Carr reference previously cited by the Examiner; the Claims meet the written description requirement; and the Claims do not contain new matter. Applicants respectfully request that the Claims be passed to allowance.

2) Claim 41 is Not Anticipated


The Examiner has rejected Claim 41, under 35 U.S.C. §102(a), as allegedly being anticipated by Estell (WO 99/53078). Furthermore, the Examiner argues that the parent application (U.S. Patent Appln. Ser. No. 09/060,872) does not provide descriptive support for the *Markush* group in the present Claim. Applicants must respectfully disagree with the Examiner's arguments. Nonetheless, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended Claim 41, such that "protease" is not included in the *Markush* group. As the Examiner has focused his arguments on the discussion of modified proteases in the Estell WO publication, Applicants submit that deletion of "proteases" in Claim 41 is sufficient to remove this rejection, particularly since the Examiner previously repeatedly indicated that Claim 41 is allowable. As the Estell (WO 99/53078) does not anticipate pending Claim 41, Applicants respectfully request that this rejection be withdrawn and the Claim be passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Office Action of December 19, 2003, having been addressed, reconsideration of the application is respectfully requested. Applicants respectfully submit that the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

Date: 12 January 2004


Kamrin T. MacKnight
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-5838
Fax: 650-845-6504

APPENDIX 1

Principles of Biochemistry

ALBERT L. LEHNINGER

THE JOHNS HOPKINS UNIVERSITY

SCHOOL OF MEDICINE

WORTH PUBLISHERS, INC.

FOR JAN

Principles of Biochemistry

Copyright © 1982 by Worth Publishers, Inc.

All rights reserved

Printed in the United States of America

Library of Congress Catalog Card No. 82-70015

ISBN: 0-87901-136-X

First printing, April 1982

Editors: Sally Anderson, June Fox

Production: Kenneth Ekkens

Illustrator: Shirley Baty

Picture Editor: Anne Feldman

Design: Malcolm Gear Designers

Typographer: Progressive Typographers, Inc.

Printing and Binding: Rand McNally and Company

Cover: Computer graphics representation of
bovine trypsin inhibitor-trypsin complex
(inhibitor surface in red, trypsin surface
in green), courtesy of Robert Langridge

Worth Publishers, Inc.

444 Park Avenue South

New York, New York 10016

Histones: The group of five basic proteins associated with the chromosomes of all eukaryotic cells.

Homologous protein: A protein having identical functions and similar properties in different species; e.g., the hemoglobins.

Homotropic enzyme: An allosteric enzyme that utilizes its substrate as a modulator.

Hormone: A chemical substance that is synthesized in trace amounts by an endocrine tissue and that acts as a messenger to regulate the function of another tissue or organ.

Hormone receptor: A specific hormone-binding site on the cell surface or within the cell.

Hydrogen bond: A weak electrostatic attraction between one electronegative atom and a hydrogen atom covalently linked to a second electronegative atom.

Hydrolysis: Cleavage of a molecule into two or more smaller molecules by reaction with water.

Hydronium ion: The hydrated hydrogen ion (H_3O^+).

Hydrophilic: "Water-loving"; said of polar or charged molecules or groups that associate with H_2O .

Hydrophobic: "Water-hating"; said of nonpolar molecules or groups that are insoluble in water.

Hydrophobic interactions: The association of nonpolar groups with each other in aqueous systems because of the tendency of the surrounding water molecules to seek their most stable state.

Hyperchromic effect: The large increase in light absorption at 260 nm occurring as a double-helical DNA is melted.

Immune response: The capacity of a vertebrate to generate antibodies to an antigen, a macromolecule foreign to it.

Immunoglobulin: An antibody protein generated to a specific antigen.

Induced enzyme: An enzyme that is not made by the cell (i.e., is repressed) unless it is induced by its substrate or a closely related compound.

Induced fit: A change in the shape of an enzyme to conform to the structure of its substrate.

Inducer: A molecule capable of inducing the synthesis of a given enzyme; usually the enzyme's substrate.

Informational molecules: Molecules containing information in the form of specific sequences of different building blocks; they include proteins and nucleic acids.

Initiation codon: AUG. It codes for the first amino acid in a polypeptide sequence, which is N-formylmethionine in prokaryotes and methionine in eukaryotes.

Initiation complex: A complex of a ribosome with an mRNA and the initiating Met-tRNA^{Met} or fMet-tRNA^{fMet}, ready for the elongation steps.

Initiation factors: Specific proteins required to initiate synthesis of a polypeptide by ribosomes.

Insertion mutation: A mutation caused by insertion of an extra base or a mutagen between two successive bases in DNA.

Insertion sequence: Specific base sequences at either end of a transposable segment of DNA.

Intercalating mutagen: A mutagen that inserts itself between two successive nucleotides and causes a frame-shift mutation.

Interferon: A protein made by virus-infected cells of vertebrates; it prevents infection by a second kind of virus.

Intermediary metabolism: In cells, the enzyme-catalyzed reactions that extract chemical energy from nutrient molecules and utilize it to synthesize and assemble cell components.

Intron: An intervening sequence in a gene; it is transcribed but excised before the gene is translated.

In vitro: "In glass," i.e., in the test tube.

In vivo: "In life," i.e., in the cell or organism.

Ion-exchange resin: A polymeric resin that contains fixed charged groups and is used in chromatographic columns to separate ionic compounds.

Ionizing radiation: A type of radiation, such as x-rays, that causes loss of electrons from some organic molecules, thus making them more reactive.

Ion product of water: $K_w = [\text{H}^+][\text{OH}^-] = 1 \times 10^{-14}$ at 25°C.

Irreversible process: A process in which the entropy of the universe increases.

Isoelectric pH: The pH at which a solute has no net electrical charge.

Isomerase: An enzyme catalyzing transformation of a compound into its positional isomer.

Isoprene: The hydrocarbon 2-methyl-1,3-butadiene, a recurring structural unit of the terpenoid biomolecules.

Isothermal process: A process occurring at constant temperature.

Isotopes: Stable or radioactive forms of an element that differ in atomic weight but are otherwise chemically identical with the naturally abundant form of the element; used as tracers.

Isozymes (isoenzymes): Multiple forms of an enzyme that differ from each other in their substrate affinity, in their maximum activity, or in regulatory properties.

K_M : See Michaelis constant.

Keratins: Insoluble protective or structural proteins consisting of parallel polypeptide chains in α -helical or β conformations.

Ketogenic amino acids: Amino acids whose carbon skeletons can be precursors of the ketone bodies.

Ketone bodies: Acetoacetate, D- β -hydroxybutyrate, and acetone, products of partial oxidation of fatty acids.

Ketose: A simple monosaccharide having its carbonyl group at other than a terminal position.

Ketosis: A condition in which the ketone body concentration of the blood, tissues, and urine is abnormally high.

Kinase: An enzyme catalyzing phosphorylation of an acceptor molecule by ATP.

APPENDIX 2

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THE PENGUIN DICTIONARY OF
CHEMISTRY

Second Edition

Edited by D. W. A. SHARP, M.A., PH.D.,
C.CHEM., F.R.S.C., F.R.S.E.



PENGUIN BOOKS

PENGUIN BOOKS

Published by the Penguin Group

Penguin Books Ltd, 27 Wrights Lane, London W8 5TZ, England

Penguin Books USA Inc., 375 Hudson Street, New York, New York 10014, USA

Penguin Books Australia Ltd, Ringwood, Victoria, Australia

Penguin Books Canada Ltd, 10 Alcorn Avenue, Toronto, Ontario, Canada M4V 3B2

Penguin Books (NZ) Ltd, 182-190 Wairau Road, Auckland 10, New Zealand

Penguin Books Ltd, Registered Offices: Harmondsworth, Middlesex, England

An abridged edition of *Miall's Dictionary of Chemistry 5th Edition*,
edited by Professor D. W. A. Sharp, first published by Longman Group Ltd, 1981

First published in Great Britain by Penguin Books 1983

Second edition 1990

3 5 7 9 10 8 6 4

Fifth Edition of *Miall's Dictionary of Chemistry* copyright © Longman Group Ltd, 1981

This adaptation copyright © Penguin Books Ltd, 1983, 1990

All rights reserved

Printed in England by Clays Ltd, St Ives plc

Set in Monophoto Times

Except in the United States of America, this book is sold subject
to the condition that it shall not, by way of trade or otherwise, be lent,
re-sold, hired out, or otherwise circulated without the publisher's
prior consent in any form of binding or cover other than that in
which it is published and without a similar condition including this
condition being imposed on the subsequent purchaser

In this Dictionary I
various branches of
and chemical operati
universities from the
college. We have nec
chemicals met with a

We have paid par
some indication of tl
relative magnitudes
this, because of avail
common data or co
used as seem most a
many speciality chen

The nomenclature
in context by users
nomenclature is use
used. Cross-referenc

The list of contril
they who originally
Dictionary has been
would appreciate re

Department of Cher
University of Glasg
Glasgow G12 8QQ

lower alcohols are boiled with alcohols of greater molecular weight. *See* acetals.

keten, $\text{CH}_2\text{:CO}$. A colourless gas, manufactured by passing propanone rapidly through metallic tubes heated at $550\text{--}800^\circ\text{C}$, or by heating ethanoic acid at $700\text{--}1000^\circ\text{C}$. It is very unstable and dimerizes spontaneously to diketene. Reacts with water to form ethanoic acid, with alcohols to give ethanoates, with ethanoic acid to give ethanoic anhydride and with amines to give acetyl derivatives. Used as an acetylating agent, particularly in the manufacture of cellulose acetate.

ketens Organic compounds containing the group >C=C=O . They are formed by the action of zinc powder on the acid bromide or chloride of an α -bromo- or α -chloro-fatty acid, or by heating the anhydride of a dibasic acid. Ketene itself and other ketens containing the group --CH=C=O are colourless substances. The remaining ketens are highly coloured. Both types react readily with water to give acids, with alcohols to give esters and with halogens and halogen acids.

keto- A prefix used to denote that the substance in question contains a carbon atom attached to an oxygen atom by a double bond and to two other carbon atoms by single bonds.

ketols Organic compounds containing both a keto- and an alcohol group. They are formed by oxidation of glycols or by condensation between two molecules of a ketone. They exhibit the typical properties of both alcohols and ketones.

ketomalonic acid *See* mesoxalic acid.

ketone bodies, **acetone bodies** The ketone bodies, propanone (acetone), CH_3COCH_3 , acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$ and β -hydroxybutyric acid, $\text{CH}_3\text{CHOHCH}_2\text{COOH}$, are excreted in the urine in severe cases of diabetes.

ketones Organic compounds containing the C-CO-C group. They include aliphatic, aromatic, cyclic and mixed ketones. The cyclic ketones have the carbon of the carbonyl group as part of a ring. They are formed by the dry distillation of the calcium or barium salts of acids, or by passing the acids over ThO_2 at 400°C . Ketones may be obtained by oxidation of secondary alcohols. Aromatic and mixed ketones are usually prepared by Friedel-Crafts reaction using acyl halides. Aliphatic ketones are usually liquids and aromatic ketones solids, they have ethereal or aromatic odours. They are reduced to secondary alcohols, but are

resistant to oxidation and give mixtures of acids and other products when strongly oxidized. They form oximes with hydroxylamine, hydrazones with hydrazine and substituted hydrazines, and semicarbazones with semicarbazide. Isonitrosoketones are formed by the action of sodium nitrite.

ketose A ketose is a sugar containing a potential keto- (CO) group. The presence of the group may be obscured by its inclusion in a ring system. Ketoses are called ketopentoses, ketohexoses, etc., according to the number of carbon atoms they contain.

ketoximes Organic substances containing the group >C=NOH . They are formed by treating ketones with hydroxylamine. They are similar in properties to the aldoximes, but undergo the Beckmann rearrangement when treated with sulphuric acid. They are reduced to primary amines.

ketys, e.g. $\text{K}^+(\text{OCPh}_3)^-$. Salts of radical anions of ketones, intensely coloured; dimerize readily.

Kevlar An aramide fibre.

kieselguhr *See* diatomite.

kinase Any enzyme catalysing the transfer of phosphate from ATP to the indicated substrate, e.g. hexokinase (transfer to hexose).

kinetics, chemical The branch of chemistry which is concerned with the explanation of observed characteristics of chemical reactions (e.g. the variation of reaction velocities with pressure, temperature or concentration).

kinetic theory of gases The theory in which the properties of gases are derived by applying the laws of probability and of particle dynamics to a system in which the gas is assumed to consist of elastic particles possessing temperature-dependent, random motion.

Kipp's apparatus Equipment for the production of a gas by interaction of a liquid and a solid. It consists of three receptacles, the top is reservoir for the liquid and is connected to the bottom. The middle contains the solid and a tap for the gas. When gas is released the liquid rises and reacts with the solid, when the tap is closed the back pressure returns the liquid to the lower reservoir and reaction ceases. Once widely used for the production of H_2S (HCl and FeS) and CO_2 (HCl and CaCO_3).

Kirchhoff's equation If Q is the heat evolved when a process (physical or chemical) is carried out at temperature T , the heat which would be evolved if the same process were carried out at

a different temperature T' is given by Kirchhoff's

$$dQ/dT = C_1 - C_2$$

where C_1 and C_2 are the heat capacities of the system before and after the reaction respectively (e.g. reactants and products of a chemical reaction). K is the direct consequence of thermodynamics.

Kjeldahl method A method for the determination of nitrogen in organic materials. The sample is digested with NH_4^+ with concentrated H_2SO_4 . After neutralization with alkali, the ammonia is estimated by titration.

knocking Both spark-ignition and compression-ignition engines suffer from knocking because of explosive combustion. Knocking is normally a function of engine speed, compression ratio, fuel, and knock rating.

knock rating The ten percent knock rating is the octane number of a diesel fuel to produce knocking.

Knudsen cell *See* effusion cell.

Kohlrausch equation Describes the behavior of electrolytes on dilution, states that

$$\Lambda_{\infty} - \Lambda = C$$

where Λ_{∞} is the equivalent conductance at infinite dilution, Λ the equivalent conductance at concentration C is the electrolyte. The equation is valid for dilutions.

Kolbe reaction The electrolysis of solutions of phatic carboxylic acid gives ethane.



and succinic acid gives

APPENDIX 3

Drug Name/Type	Important Features
Muscarinic Agonist	
Metocholine	Diagnosis of asthma
Carbachol	Miosis in ophthalmic surgery
Bethanechol	Urinary retention (effects on GI/GU tracts), paralysis of GI tract
Pilocarpine	Treat open (wide)-angle glaucoma
Muscarinic Antagonists	Reduce salivary, bronchial and sweat secretion, pupil, ciliary muscle and cardiac vagus, urinary bladder, GI tract and bronchi and gastric secretion (from most effects to least)
Atropine	Excite respiration, restlessness and irritability (at high doses, hallucinations and delirium) Antidote: Physostigmine
Scopolamine	Drowsiness, sleep, hallucinations and delirium
Glycopyrrolate	Preanesthetic to inhibit excess salivation by other anesth.
Ipratropium Bromide	Dilate bronchial airways (less drying than atropine)
Nicotinic Agonists	
Nicotine	Stimulates autonomic ganglia, parasympathetic and sympathetic, increases BP, increased GI motility, no tolerance to cardiac effects. Stimulates respiration, causes emesis, tremors, convulsions, addiction, NMJ
Nicotinic Antagonists	Not used anymore
Curare	Lots of histamine release
Cisatracium	
Rocuronium	Decreased heart rate
Mivacurium	
Cholinesterase Inhibitors	Miosis of eye, GI contractions, stimulations skeletal muscle, exocrine glands, bronchi contract, bradycardia/ fall in CO, treat toxicity with atropine and pralidoxime
Physostigmine	Glaucoma, atropine poisoning, alzheimer's Dz
Edrophonium	Termination of NMJ blockade, SHORT T1/2
Neostigmine	Paralytic ileus and urinary retention, terminate NMJ blockade, MG
Pyridostigmine	Myasthenia gravis
Neuromuscular Blocking Agents	Charged, no CNS effects, some cause histamine release, fast onset when IV
Curare	Affect autonomic ganglia
Gallamine	Affect autonomic ganglia
Pancuronium	Does not affect AG
Depolarizing Agents	Nicotinic agonists, 2 phases of blockade, Phase I is reversible, Phase II is less so, IV, can cause respiratory arrest in overdose, used as muscle relaxants in surgery; can cause malignant hyperthermia
Succinylcholine	Stimulates vagal and sympathetic ganglia, bradycardia and hypotension or the reverse can be seen, onset 1-2 minutes, duration 5 min, significant histamine release
Decamethonium	No effect on AG

Adrenergic Agonists	
α_1	Constrict arteries and veins (increases peripheral resistance), dilate eye, contract uterus, muscarinic stimulation, GH release, PHENYLEPHRINE, G \rightarrow PLC \rightarrow \uparrow Ca ²⁺
α_2	Relaxes arteries via neurons, relaxes GI, inhibits secretion, CLONIDINE, G _i \rightarrow inhibits Adenylate cyclase \rightarrow \downarrow cAMP
β_1	Increase all cardiac (force more than rate), stimulates rennin, DOBUTAMINE, G _s \rightarrow Adenylate cyclase \rightarrow \uparrow cAMP
β_2	Dilates arteries in skeletal muscle (decreased peripheral resistance), dilates bronchioles, relaxes GI, inhibits secretion, relaxes uterus, stimulates insulin release, inhibits GH release, inhibits histamine release, TERBUTALINE, G _s \rightarrow Adenylate cyclase \rightarrow \uparrow cAMP
Norepinephrine	α_1 , α_2 , β_1 (selective for arterial constriction, increase heart rate, contract uterus, dilate eye), will decrease HR due to reflex to vasoconstriction, BP elevated
Epinephrine	α_1 , α_2 , β_1 β_2 (non-selective), parenteral only, will increase pulse pressure the most, raise HR, strong bronchodilation via β_2 , used to "restart" heart after heart attack by improving conduction, used in acute anaphylaxis, wide-angle glaucoma
Isoproterenol	β_1 , β_2 (selective β), will decrease BP after short increase (reflex), raise HR significantly, strong bronchodilation via β_2
Dopamine	β_1 , α at high doses, useful as an inotropic agent for failing hearts by increasing force more than rate, used in shock to reduce arterial resistance to blood flow to the kidney and preserve kidney function
*Dobutamine	β_1 , useful as an inotropic agent for failing hearts by increasing force more than rate
Amphetamine	Mixed action, oral, marked CNS effects
Ephedrine	Mixed action, oral, long T _{1/2} , marked CNS effects, midriasis in ophthalmology
*Phenylephrine	α_1 , primary effect on peripheral vasculature, will increase BP the most but decrease HR by reflex, uterine contraction, midriasis in ophthalmology, wide-angle glaucoma
*Terbutaline	β_2 , strong bronchodilation, uterine relaxation
Albuterol	β_2 , strong bronchodilation
Ritodrine	β_2 , uterine relaxation
Tyramine	Indirect acting, not prescribed
*Clonidine	α_2 , inhibits insulin secretion, used to treat hypertension by dilating arteries

Adrenergic Antagonists	α - Postural Hypotension, sedation/depression, increased GI motility, sodium retention, impaired sexual function β - no therapeutic differences in treatment of angina or hypertension, but there are pharmacological differences
Phentolamine	α 1, α 2, Used before epinephrine, it reduces the BP effects but not the HR, used after it has no effect, reversible, competitive, IV only, vasodilation via direct action, direct cardiac stimulation, surgery for pheochromocytoma
Ergot Alkaloids	α -receptor blocker but exhibit profound uterine contractions by stimulating α 1 receptors in uterus
Phenoxybenzamine	α 1, α 2, irreversible, develops slowly and is long lasting, decreased BP, reflex increase in HR, enters CNS, IV usually, oral for pheochromocytoma before surgery or for chronic treatment
Prazosin	α 1, competitive, vasodilation w/o reflex tachycardia, post hypotension only with first dose, chronic admin leads to fluid retention via decreased GFR, little GI stim, rarely produces sexual dysfunction, CNS effects, oral 1-3pd, liver met, used for essential hypertension
Terazosin	α 1, analog of prazosin, longer half life, oral qd, used for urinary retention, ess hypertension
Propanolol	β 1, β 2, decreased systolic pressure, rate, O_2 consumption can cause heart block, failure, increased peripheral resistance and decreased tissue perfusion, decreased rennin, increased exercise tolerance, increased airway resistance BEWARE ASTHMATICS, blockade of insulin release and sensitization, CNS effects including nightmare and insomnia/depression, oral but with high first pass metabolism, liver met, high protein bound, serious withdrawal can cause sudden death
Nadolol	β 1, β 2, longer half life
Timolol	β 1, β 2, glaucoma in one formulation by reducing aqueous humor
Pindolol	β 1, β 2, partial agonist less withdrawal
Labetolol	α and β 1, β 2, all side-effects
Metoprolol	β 1, competitive, needs high doses to cause broncho-constriction
Atenolol	β 1, no intrinsic sympathomimetic activity, little CNS, slightly longer half-life
Acebutolol	β 1, ophthalmic use, short half-life
Esmolol	β 1, very short acting, very short half-life (10 minutes), IV for critically ill patients, SVT, no intrinsic activity
Betaxolol	β 1, glaucoma, ophthalmic use, less bronchoconstriction, for hypertension
Adrenergic Blocking Agents	Very effective with lots of side effects, therapy is VERY restricted
Guanethidine	Blocks exocytosis of NE, replaces NE in vesicles, serious sexual dysfunction, spares adrenal medulla, causes severe receptor

	supersensitivity, can cause severe ortho-static hypotension, oral only, no CNS, kidney excretion, always used with a diuretic
Reserpine	Can cause profound depression and suicide, depletes catecholamine stores centrally and peripherally, blocks uptake of amines into storage, blocks cardiovascular reflexes, parasympathetic predominance

Eicosinoids, NSAIDs, etc

Eicosinoids	
Thromboxane A ₂ (TXA ₂)	Short-lived (30s), platelet aggregation
Prostaglandin I ₂ (PGI ₂)	Short-lived (3m), antagonist of TXA ₂ , made in vessel wall, maintains PDA, relaxes BSM, vasodilation), prominent hypotension, pain, cytoprotective in GI
Prostaglandin E ₂ (PGE ₂)	Uterine contraction, potent vasodilation, inhibit ADH, pain, cytoprotective in GI
Prostaglandin F _{2α} (PGF _{2α})	Formed from PGE ₂ , uterine contraction, constricts BSM, constricts pulmonary A+V
Prostaglandin D ₂ (PGD ₂)	Constricts BSM, dose related vessel effects (low=vasodilation)
Leukotriene B ₄ (LTB ₄)	Pain, PMN attractant
Leukotriene C ₄ (LTC ₄)	Most potent bronchoconstrictor (BSM) known
Leukotriene D ₄ (LTD ₄)	Constricts BSM
Leukotriene E ₄ (LTE ₄)	
Misoprostol	PGE ₁ analog, adjuvant to NSAID therapy for GI protection, CI in pregnancy
Carboprost	15-methyl-PGF _{2α} , induce abortion, smooth muscle contraction
Dinoprostone	PGE ₂ , promotes cervical ripening, induces labor, abortion
NSAIDs	Reduce fever-inhibit production of PGs in hypothalamus, reduce inflammation- inhibit formation of PGE ₂ and PGI ₂ , reduce pain-inhibit production of PGE ₂ and PGI ₂
Celecoxib	COX2, pain RA, OA, fewer GI effects, T _{1/2} =11h, 5d to steady state, CI in pts with allergy to aspirin or sulfonamides
Rofecoxib	COX2, steady state in 4 days, CI in pts with Aspirin allergy
Aspirin	Upper GI absorption, variable T _{1/2} , irreversibly inhibits COX1, high doses-stimulate respiration, CNS effects including respiratory depression (paradoxical) and uncompensated respiratory acidosis, variable effects on uric acid secretion (low=inhibit)
Salicylic acid	Topical use to treat warts and corns
Acetaminophen	Few anti-inflammatory effects, oral T _{1/2} =2h, hep met, used as anti-pyretic, at high doses, saturates glutathione and prevents metabolism of other toxins, antidote is N-acetylcysteine
Indomethacin	Indole. Oral, T _{1/2} =3h, hep met, 90% bound, lots of SE, fever in Hodgkin's Dz, ankylosing spondylitis, osteoarthritis, DOC in gout, prevents premature labor but can close PDA
Sulindac	Indole. Active metabolites 500x more potent than Indo, longer

	half life (7h or 18h for metabolites), fewer GI and renal SE, used for RA, OA, Ankylosing S.
Tolmetin	Heteroacyl AA. Used for RA, OA, AS, does not interfere with Warfarin, GI SE, anaphylactic response in some
Ketorolac	Heteroacyl AA. Very potent analgesic with hi GI tox, postoperative pain-IV
Mefenamic Acid	Fenemate. Analgesia, not used much-causes diarrhea
Ibuprofen	Propionic Acid derivatives. Used for RA, OA, AS. Short $T_{1/2}$, treats dysmenorrhea, CI in pregnancy/nursing
Naproxen	PAD, Long $T_{1/2}$, DOC in gout
Phenylbutazone	Pyrazolan derivative. More potent anti-inflammatory than aspirin, serious SE incl fatal bone marrow suppression, uricosuric, can displace other drugs from plasma proteins
Sulfinpyrazone	Metabolite of phenylbutazone used for gout due to high uricosuric property
Apazone	New pyrazolan with fewer side-effects
Piroxicam	RA, OA (equivalent to aspirin, etc.) LONG half life, qd
Aurothioglucose	IM for RA, kidney damage
Auranofin	Oral for RA, kidney damage
Gold Sodium Thiomalate	Treatment of RA, not used for acute inflammation or pain, IM, can cause kidney damage
Cochicine	From the autumn crocus, binds to tubulin and inhibits polymerization and mitosis, oral or IV, excreted in bile, LONG half-life, SE: GI and bone marrow suppression, CNS paralysis
Allopurinol	Xanthine Oxidase Inhibitor, decreases formation of uric acid with short $T_{1/2}$, effect lasts longer, can ppt attack
Probenecid	Net increase in elimination of UA, CI in pts with peptic ulcers

Histamine and Bradykinin	
First Generation Histamine (H₁) Blockers	More lipid soluble, rapidly absorbed, hep met, effective for 4-6 hours, wide distributed including CNS, block edema and itch well but not Bronchoconstriction, antitussive, antiemetic
Diphenhydramine	
Chlorpheniramine	
Pyrilamine	
Promethazin	
Meclizine	
Second Generation H₁ Blockers	Less lipid soluble, no CNS, effective 12-24 hours, not anti-cholinergic
Terfenadine	Can cause cardiac arrhythmias, beware using with macrolides and antifungals (use up CYP3A4), prolong QT interval
Astemizole	Can cause cardiac arrhythmias by above mechanism
Fexofenidine	
Loratidine	
Bradykinin	Vasodilation, increased permeability, smooth muscle contraction, pain producing, mast cell activation
Ipratropium Bromide	Muscarinic Receptor Antagonist, block ACh mediated contraction of BSM, competitive inhibitor, inhaled, no CNS SE like precursor atropine
Thiophylline	Methylxanthine, oral treatment of asthma, bronchial dilation, inhibits mast cell degranulation, inhibits phosphodiesterase, ↑cAMP, inhibits adenosine receptors, serious SE incl CNS and cardiac stimulation, weak diuretic, increase contraction of skeletal muscle
Aminophylline	Like thiophylline, remember uses CYP3A4 like H blockers
Cromolyn Sodium	Prophylaxis only, inhibit mast cell degranulation, no bronchial dilation, 2-4wks before effect, works for few
Nedocromil Sodium	Same as Cromolyn
Ephedrine	OTC asthma med used for acute attack
Beclomethasone	Glucocorticoid, anti inflammatory for prophylaxis or for treatment of inflammatory response with severe attack, inhibit PLA ₂ , thus reducing synthesis of leukotrienes and prostaglandins, few SEs for inhaled preps
Fluticasone	Glucocorticoid, inhaled
Flunisolide	Glucocorticoid, inhaled
Prednisone	Glucocorticoid, oral preparation for severe exacerbations, lots of SEs
Zafirlukast	LTD ₄ antagonist, with some LTC ₄ , LTE ₄ . NO LTB ₄ , prevent bronchospasms, SE of increasing liver enzymes
Montelukast	Same as Zafirlukast, these block receptors not formation
Zileuton	Blocks formation of all leukotrienes, SEs include increasing liver enzymes but inhibiting CYP3A4

Immunosuppressive Agents	
Cyclosporine A	Used in transplant, targets calcineurin in T cells and inhibits function, Fungal origin, IV/oral, biliary excretion mostly, P450, renal toxicity
Tacrolimus	Transplant, 100x more potent than Cyclosporine A, Bacterial origin, IV/oral, targets leukocytes, longer action, also nephrotoxic, target T cells FKBP inhibits function
Corticosteroids	Suppresses the production of cytokines at the gene level, thus they are not immediate
Cortisol (hydrocortisone)	Activates gluconeogenesis in liver, protein breakdown, lipolysis, inhibits glycolysis, can exacerbate hyperglycemia, redistributes body fat to face, neck, enhances action of β -adrenergics and GH to promote lipolysis, needed for skeletal muscle function, hypertension, improve awareness; effects behavior and mood, suppresses number of WBCs all cells except PMNs and inhibits cytokine production, inhibits PLA ₂ , 1x anti-inflammatory potency, 1x Na ⁺ retaining potency, short duration, used for adrenal cortical insufficiency, some anti-inflammatory, binds to glucocorticoid and mineralocorticoid receptors but is inactivated at MC receptor by 11- β hydroxysteroid dehydrogenase. Metabolic and AI/IS effects are through GC receptor
Cortisone	.8x AI potency, .8x NR potency, short duration
Fludrocortisone	10x AI potency, 125x NR potency, short, replacement therapy in Addison's Dz
Prednisone	4x AI potency, .8x NR potency, intermediate, Addison's and AI/immunosuppression, used with Tacrolimus or Cyclosporine for transplant to reduce nephrotoxicity, serious withdrawal, fluid/electrolyte abnormalities, hypertension, hyperglycemia, osteoporosis, IS, myopathy, behavioral disturbances, cataracts, growth arrest, fat redistribution, peptic ulcer risk
Prednisolone	4x AI potency, .8x NR potency, intermediate, same as prednisone
6 α -methylprednisone	5x AI potency, .5x NR potency, intermediate, AI/IS
Triamcinolone	5x AI potency, 0 NR potency, intermediate, AI/IS
Betamethasone	25x AI potency, 0 NR potency, long duration, AI/IS
Dexamethasone	25x AI potency, 0 NR potency, long duration, AI/IS
Cytotoxic agents	Prevent clonal expansion of T and B cells
Azathioprine	Purine antimetabolite, oral or IV, used with cyclosporine or Tacrolimus in transplant, affects all rapidly dividing cells
Mycophenolate Mofetil	Prodrug, inhibits purine synthesis, does not affect salvage pathway (affects B and T cells more than others), oral, used in kidney transplant
Cyclophosphamide	Alkylating agent, B > T cells, oral, short term
Methotrexate	Inhibits DHFR, inhibits synthesis of B and T cells, used in autoimmune Dz (lower doses than chemo)

GI Drugs	
Antacids	Most contain $\text{Al}(\text{OH}_3)$ and $\text{Mg}(\text{OH}_2)$, Al can cause constipation, Mg can cause laxation, Mg prevails at higher doses, can cause alkalosis, formulas with Ca can cause gas
Cimetidine (Tagemet)	Act on H_2 receptors on parietal cells, blocks histamine stimulated release of acid, antiandrogen, interferes with CytP450, greatest effects on basal secretion,
Ranitidine	Like cimetidine, used more often because it is more potent and interferes less with CytP450, longer acting,
Famotidine	
Esomeprazole	Acts on H^+/K^+ ATPase on parietal cells, very effective, long lasting (1 day), Prodrug activated by H^+ , S isomer, may interfere with liver enzyme function, can cause increased colonization of stomach, headaches, flatulence, respiratory infections, sinusitis, stimulates gastrin over long term, time req'd for healing is the least of all drugs used for this purpose, does not effect H. pylori, use Abx,
Lansoprazole	Part of alternate triple therapy of Lansoprazole, metronidazole, clariethromycin, alternative to esomeprozole
Metoclopramide	Promote gastric emptying and contraction of LES, anti-emetics, act on neurons- cholinergic stimulation, dopamine antagonist, at high doses-5HT ₃ antagonist
Cisapride	5-HT ₄ agonist stimulates myenteric plexus, no anti-dopamine, 5-HT ₃ antagonist-blocks emesis, effects may reach colon (unlike metoclopramide), can be used with chemo drugs to block emesis
Ondansetron	5-HT ₃ antagonist- blocks emesis produced by chemo drugs
Bismuth Subcitrate	Treats traveler's diarrhea, antibiotic
Bisacodyl	Promote accumulation of fluid and electrolytes in the lumen, may incite an inflammatory response, very limited use despite OTC use
MgSO_4	Saline laxative, exerts "osmotic" effect, used to empty bowel before surgery or after chemo
Mythylcellulose	Bulk-forming laxative like bran, softening stools
Diphenoxylate	Slows transit time, "local" effects due to retaining in the GI tract, treats acute diarrhea, not used for infectious or inflammatory diarrhea, opioid
Sucralfate	Act on mucosal surface, adheres to ulcerated crater, $\text{Al}(\text{OH}_3)$ and sulfated sucrose, 6h, can cause constipation,
Bismuth	Act on mucosal surface, bactericidal, retards H^+ diffusion to mucosa, part of triple therapy of Bismuth, metronidazole and Tetracycline
Misoprostol	Act on mucosal surface, PGE_1 , inhibits Adenylate cyclase complex and acid secretion, can cause abdominal pain/ uterine contractions- CI in pregnancy

Diuretics	
Acetazolamide	CAI, LUMEN LESS POSITIVE, inhibits H^+ secretion - PT, TAL, DT; inhibits HCO_3^- reabsorption; urinary: $\uparrow Na^+$, $\downarrow\downarrow Cl^-$, $\uparrow\uparrow HCO_3^-$, $\uparrow K^+$, metabolic acidosis, $\uparrow Ca^{++}$, 3x \uparrow in volume; acidosis decreases efficacy, secreted via organic anion transporter, used to treat glaucoma, alkalosis or to \uparrow excretion of uric acid or cysteine., can cause renal stones and potassium wasting
Furosemide	Loop diuretic, LUMEN LESS POSITIVE, compete for Cl^- on Na-K-2Cl cotransporter, $\uparrow Na^+$, $\uparrow Cl^-$, $\downarrow HCO_3^-$, $\uparrow K^+$, metabolic alkalosis, $\uparrow Mg^{++}$, $\uparrow Ca^{++}$, 8x \uparrow in volume, nephron cannot concentrate urine, no hypocalcemia, venous capacitance \uparrow , short half life, bound, secreted by OAT in PT; used in ARF or edema by CHF, hypercalcemia, mild hyperkalemia or severe hyponatremia (w/ hypertonic saline); can cause hyperuricemia, hypomagnesemia, dehydration, hyperglycemia, ototoxicity or hypokalemic metabolic alkalosis
Bumetidinide	Loop diuretic, same as above
Ethacrynic acid	Loop diuretic, also inhibits basolateral K-Cl symporter, same as above
Hydrochlorothiazide	Thiazide, early distal tubule, INTRACELLULAR NEGATIVE (LUMEN POSITIVE), Compete with Cl^- on Na/Cl cotransporter, $\uparrow Na^+$, $\uparrow Cl^-$, $\downarrow HCO_3^-$ (CCT), $\uparrow K^+$ (most) by CCT, $\downarrow Ca^{++}$, metabolic alkalosis, 3x \uparrow in volume, reliant on GFR, inhibit carbonic anhydrase, used for HTN, reduces PVR, for hypercalciuria, enhances proximal reabsorption – for DI, can cause hypokalemia by increasing Na^+ delivery to the CCD in the presence of little Ca^{++} - need K^+ supplements, hyperglycemia, hyponatremia – by enhancing ADH secretion, hyperuricemia- by enhanced PT reabsorption, hyperlipidemia, hypercalcemia, intermediate acting, action more dependent on GFR than furosemide but still uses OAT
Chlorthalidone	Thiazide, long acting
Metolazone	Thiazide, intermediate acting
Indapimide	Thiazide, long acting
Potassium	Supplements needed with thiazides
Triamterene	K-sparing diuretic, direct inhibition of electrogenic Na^+ entry, oral, OAT, bound, extensively metabolized, shorter duration, nephrotoxicity, interferes with hematopoiesis
Amiloride	K-sparing diuretic, like triamterene, not metabolized, shorter duration
Spironolactone	K-sparing diuretic, antagonist of aldosterone, $\uparrow Na^+$, $\uparrow Cl^-$, $\downarrow H^+$, $\uparrow HCO_3^-$, $\downarrow K^+$, 2x urine volume, efficacy depends on aldosterone levels, bound, slow action but longer duration, used

	to prevent K ⁺ wasting with other D, Mineralocorticoid excess, aldosteronism in CHF, RF (edema), can cause hyperkalemia, CI with ACEI, renal insufficiency, can cause gynecomastia
--	---

Anticlotting drugs	
Anticoagulants	
Heparin	IV, stimulates ATIII, blocks Domains I, II, III – thrombin (IIa), Factor VIIa, IXa, Xa, forms Heparin-ATIII complex , most effective in prevention, treat OD with protamine sulfate, can cause TCP, long term can cause osteoporosis, loading dose
LMW Heparin	IV, just domain I (Xa) , used for DVT, lower risk of thrombocytopenia, but it still exists
Hirudin	IV, independent of ATIII, used for heparin-induced TCP
Bivalirudin	IV, direct thrombin inhibitor, used with aspirin in pts undergoing PTCA for unstable angina
Argatroban	Direct thrombin inhibitor, IV, for heparin-induced TCP
Warfarin	Oral, prevention, recemic or as S-warfarin (4x more potent), blocks Vit K factors (II, VII, IX, X, Protein C), affect synthesis, take a week, cyP450 met, albumin bound, can cause bleeding, OD/ Ant: give Vit K, CI in pregnancy
Fibrinolytics	
Streptokinase	Short term treatment, activates plasmin to dissolve clots, bleeding is major side effect
Anistreplase	Acetylated streptokinase + plasminogen
TPA	Produced by endothelial cells, liver clearance, loading dose
Retaplast	Recombinant TPA, longer half-life, specific for coronary thrombi
Urokinase	Cadaveric from kidneys converts plasminogen to plasmin
Anti-platelets	
Aspirin	Irreversible inhibitory of COX 1, 2, Blocks formation of TXA ₂ and PGI ₂ , can cause peptic ulcer disease and GI bleeding
Dipyridamole	Blocks phosphodiesterase, potentiates effect of Warfarin and Heparin (NOT USED ALONE),
Ticlopidine	Blocks ADP receptor, inhibits platelet aggregation, for pts allergic to aspirin , with intracoronary stents, takes a week
Clopidogrel	Irreversibly inhibits ADP receptors, takes a week
Abciximab	Antibody, Blocks GPIIb/IIIa, IV, VERY expensive
Tirofiban	IV, non-antibody GP IIb/IIIa, pts with unstable angina
Eptifibatide	GP IIb/IIIa blocker, used in PTCA, MI, angina
Aminocaproic acid	Fibrinolytic inhibitor, treats hemophilia, oral or IV

Anticholesterol Drugs	
Bile Sequestrants	Rein w/ + charged amines, Colestipol, ↑ LDL-R synthesis, ↓ LDL 20%, ↑ HDL 4%, ↔ TG, can cause GI problems, N, gas, pancreatitis (TG>200), CI in pts with TG >400, used with statins
Niacin	Cheap, often not tolerated (45%), ↓ VLDL and TG 20-50%, ↓ LDL 20%, ↑ HDL 30%, can cause gastric distress, hepatotoxicity, skin problems, hyperuricemia, arrhythmia, glucose intolerance , CI in liver disease, gout, diabetes, peptic ulcers
Statins	HMG CoA reductase competitive inhibitors, ↑ LDL-R levels, also have anti-oxidant, anti-inflammatory actions, met by CytP450, ↓ LDL 20-50%, ↓ TG 10-30%, ↑ HDL 10%, proven in studies to reduce mortality of MI, CHD, can cause rhabdomyolysis (myopathy), worse with fibrate, cyclosporine, niacin, used in <i>heterozygous</i> familial hypercholesterolemia
Lovastatin	Lower potency
Simvastatin	Intermediate potency
Pravastatin	Lower potency, not met by CytP450, excreted in urine
Atorvastatin	Most potent, not yet trial tested, but can be used for <i>homozygous</i> familial hypercholesterolemia
Fibrates	Gemfibrozil, inhibits VLDL synthesis, activate LPL, ↓ TG 20-50%, ↓ LDL-C 5-20%, ↑ HDL 15%, may raise LDLs in pts with very high TG, well tolerated, can cause gallstones, myopathy (resolves with discontinuation), ↑ LFTs, leukopenia, potentiates coumadin, GI distress, used for High TGs including Type V hyperlipoproteinemia with poor LPL function (no LPL function and the drug won't work), useful when HDL is low and LDL is high, proven to prevent MI, CI in pregnancy/nursing, severe renal or hepatic disease

Renin-Angiotensin	
ACE Inhibitors	Inhibits the conversion of Angiotensin I to Angiotensin II, elevates bradykinin and Ang I, causes vasodilation and Ang II escape, In HTN: ↓ PVR and thus ↓ BP, ↓ reflex responses, little change in GFR, ↓ Na ⁺ reabsorption, ↓ ECV, ↓ preload, ↓ CO, ↓ LVH, In CHF: ↓ afterload and preload, ↑ CO, ↓ SNA, also used in renal impairment, can cause hypotension, hyperkalemia, ARF, angioedema, cough, birth defects
Captopril	Short acting , reduced availability by food, oral, can also cause rash, altered taste, proteinuria, neutropenia, agranulocytosis
Enalapril	Prodrug, met by liver and kidney, oral
Lisinopril	Not Prodrug , poor absorption, renal elimination longer T1/2
Fosinopril	Prodrug, renal/hepatic elimination, binds tightly to ACE

Others	
Losartan potassium	Angiotensin Receptor Blocker, AT ₁ selective, oral, T _{1/2} 2h, efficacy = ACEIs, no cough, angioedema, can cause defects in pregnancy
ANP	Released on stretch, volume expansion, made in atria and stored as a prohormone, T _{1/2} = 3m, cleared by ANP-C receptor or NEP, actions by ANP-A, ANP-B, inhibits aldosterone, ADH and renin release, causes vasodilation, ↑ permeability, diuretic, ↑ GFR by ↑ RBF, ↓ Na ⁺ reabsorption, ↓ H ₂ O reabsorption,

Smooth Muscle Drugs	
Ca⁺⁺ channel blockers	
Verapamil	intermediate acting, non-selective L-type Calcium channel blocker, vasodilation: arterioles>arteries>>veins, ↓ PVR, ↓ BP, suppresses spasm, ↓ HR, ↓ conduction through AV node, ↓ contractility, ↑ myocardial blood flow, used to reduce BP in pts with LVH, IHD + HTN, for angina, after MI, for arrhythmias, can cause cardiac depression, esp w/ B-blockers, dizziness, hypotension, headache, flushing, nausea, constipation, pedal edema, reduces platelet aggregation, role in chemo
Diltiazem	intermediate acting, like Verapamil
Nimodipine	short acting DHP (more potent than V and D), selective in VSM, used after MI, can cause reflex tachycardia and increased contractility, crosses BBB
Nifedipine	intermediate acting DHP, used after MI,
Nifedipine-SR	long acting DHP, used for HTN, angina, prevent MI, slow renal failure
Amlodipine	very long acting DHP
Amylnitrate	liquid, short acting, for emergencies
Nitrates	met by liver (hepatic organic nitrate reductase), cause release of NO, rise in cGMP and thus vasodilation, veins>arteries>arterioles, ↓ end-diastolic volume, ↓ BP, no change in PVR at low dose , high doses can cause venous pooling, ↓ PVR and activate reflex mechanisms in heart, decreased PLT aggregation, used after MI, for angina, heart failure, can cause reflex tach, hypotension, headache, causes tolerance (tachyphylaxis) , withdrawal syndrome
Nitroglycerin	oily liquid, sublingual- short acting, for exercise tolerance, ointment – intermediate acting, decrease attack frequency improve exercise tolerance; transdermal patches – long acting
Isosorbide dinitrate	solid, oral, intermediate acting
Erythryl tetranitrate	long acting, oral
Pentaerythritol	long acting, oral

tetranitrate	
Sildenafil citrate (viagra)	Don't use with nitrates, oral, hep met to active compound, inhibits PDE5(VSM)>PDE6(retina)>>PDE2,3(heart), used to treat erectile dysfunction, causes release of NO during sex to increase BF to corpus cavernosum, can cause abnormal vision, headache, flushing
Hydralazine	dilates arterioles, not veins, direct inotropic effects on heart, ↓PVR, ↓MAP, strong reflex responses in heart , oral for chronic therapy, hypotensive effects persist beyond half-life due to extensive binding, used for severe hypertension, use with B-blocker, can cause an acute state like SLE, headache
Minoxidil	dilates arterioles, prodrug, induces membrane hyperpolarization thus reducing calcium influx, similar effects to hydralazine, oral, hep met, prolonged effect, used for severe hypertension, can cause excessive vasodilation, reflex responses, hirsutism
Sodium nitroprusside	IV, for hypertensive emergencies or for severe cardiac failure, dilates arteries and veins, releases NO and ↑ cGMP, ↓ PVR and venous return, ↓ BP, causes little to no reflex responses, met generates CN, can cause excessive hypotension, toxicity due to CN

Anti-anginal drugs	
Nitrates	No direct action on cardiac myocytes, decrease work and O ₂ consumption, ↓ preload, increase O ₂ supply to heart by dilating coronary arteries, also increase subendocardial perfusion
Nitroglycerine	Acute treatment of anginal attack or prophylactically
Isosorbide dinitrate	Chronic treatment, tolerance develops, add B-blocker
B-blockers	Decreases O ₂ consumption, and increases supply to heart, only used prophylactically , for exercise induced angina, reduce need for nitrates, counterindicated in Prinzmetal's A . only the four below are approved for angina, used with nitrate in LV dysfunction, post-MI, high anxiety
Propanolol	Shorter half-life
Nadolol	Longer half-life
Atenolol	Selective beta-1
Metoprolol	Selective beta-1
Ca⁺⁺ channel blockers	All are used for angina, ↓ HR leads to ↑ O ₂ supply, ↓ TPR and ↓ contractility lead to ↓ O ₂ consumption, Can use for variant angina (unlike B-blockers) or stable angina, used in patients with no tolerance to B-blockers, good for pts with normal LV function
Verapamil/Diltiazem	Don't use with B-blocker, used w/ nitrate in pts with asthma, diabetes, hyperlipidemia, coronary spasm

Nifedipine	Do not use for angina, especially for unstable angina, all DHPs are inferior to V/D for angina
Isradipine	DHP, use with B-vlocker
Felodipine	DHP, use with B-blocker

CNS Stimulants	
Amphetamine	Causes massive release of NE + DA > 5-HT , schedule II, oral base, ↑ speech/motor activity, cause paranoia at high doses, treat w/ chlorpromazine, used for narcolepsy and obesity (sibutramine)
Methylphenidate (Ritalin)	Used for ADHD
Cocaine	Blocks reuptake of DA, NE, 5-HT , SE similar to amphetamine, use neuroleptics (DA antagonists) to block SE (all except for peripheral toxic symptoms: arrhythmias)
Methylxanthines (Theophylline and caffeine)	Inhibit Adenosine A1, A2 – R + inh. PDE, cause presynaptic inh of transmitter release and postsynaptic inh, Alkaloids in tea, coffee, etc; ↑ alertness, ↑ RR, convulsions, used in primary apnea of prematurity
Nicotine	Nicotinic agonist, also effects NMJ at very high doses, causes ↑ transmitter release, can cause N/↑RR/tremor/anorexia/muscle relaxation, strong psychological dependence, high doses cause depolarizing blockade, paralysis and death, use bupropion for addiction

Antiemetics	Don't use any in pregnancy
Scopolamine	Muscarinic antagonist, prophylaxis only
Dramamine	Muscarinic/Histamine antagonist, prophylaxis only
Metoclopramide	5HT4 agonist, 5HT3 antagonist, DA antagonist , AP+NTS+VAs, can produce EPS, also prokinetic
Phenothiazine (neuroleptics)	DA blocker, Chlorpromazine, Prochlorperazine, Droperidol, relieve post surgery nausea , act on AP, can cause EPS
Ondansetron	5HT-3 on vagal afferents, NTS, AP, use w/ dexamethasone, can use with migraines
Dexamethasone	Enhances other antiemetics in chemo
Cannabinoids	GPCR, adjunct with other N-inducing drugs
Benzodiazapines	Adjunct for chemo

Antipsychotics	
Chlorpromazine	D2 receptor antagonist , α1-antagonist, cholinergic antagonist, H1 antagonist, channel blocker, rapid effects incl sedation, disinterest, delayed effect on schizo , can cause EPS (striatal effect) and later, tardive dyskinesia, oversedation, seizures (with Hx), hypotension (tolerance), NMS, low potency agent
Thioridazine	Also a low potency agent

Fluphenazine	High potency agent (lots of EPS, less other SE)
Haloperidol	High potency agent, more effective at positive symptoms than negative
Clozapine	5HT-2A in addition to D2, can cause agranulocytosis , little EPS
Olanzapine	Some EPS, TD, some orthostatic hypotension, don't use in parkinson's patients
Risperidone	Same as olanzapine

Antidepressants	
Inhibit uptake of 5-HT and/or NE, not DA	
TCAs	Strong muscarinic, histaminergic and α 1-adrenergic antagonist properties in addition to 5-HT/NE, effects take 2-3wks to develop, tremor, insomnia, sedation, mania, seizures, toxic psychosis at high doses, OH, reflex tach, quinidine like effects, cholinergic blockade, weight gain, only give pts a week's supply , used in unipolar depression and panic disorder
Imipramine	
Desipramine	Active met of Imip.
Amitriptyline	Highly sedative
Nortriptyline	Active met of Amit.
Clomipramine	Can be used for OCD
SSRIs	Selective 5-HT uptake blocker, effects take 2 wks, used with major depression, panic disorder, OCD, less effective than TCAs at severe depression
Fluoxetine (Prozac)	Long T1/2, can cause N/headache, nervousness, insomnia, fatigue, anorgasmia, do not use with MAOIs incl MAOBs ,
Sertraline	
Paroxetine	
Fluvoxetine	
MAOIs	Wine and cheese syndrome, don't use with SSRIs, MAOB (selegiline) used for parkinson's, MAOA needed for antidepressant effects

Mood Stabilizers	
Lithium	Permeates cells in place of Na^+ , inhibits phosphatase that hydrolyzes IP2 and IP1, less effect on peripheral organs, oral only, ren elim, reabs by PT 80%, increases with Na restriction, volume depletion, can cause GI problems, tremor, weakness, cardiac toxicity, lots of OD effects, be careful with diuretics and TCAs, used to treat acute manic episode, or prophylaxis, takes 5-6d
Valproic acid	Broad spectrum anticonvulsant, impairs several ion channels
Carbamazepine	Requires 2wks

Sedatives/Hypnotics	
Benzodiazepines	Must be metabolized, high apparent volume, most oral, increased T1/2 with age, positive allosteric mod of GABA Cl⁻ channels , mostly postsynaptic, no effect in the absence of GABA, do not cause CV effects or analgesia, but do cause anxiolytic, sedation, anticonvulsant, hypnosis, amnesia, ataxia, stupor, tolerance but not to anxiolytic, psychological dependence, physical dependence based on T1/2, with shorter being worse, do not use with alcohol , , used to treat insomnia
Flurazepam	Long, not for anxiety, used for insomnia, tolerance may be balanced by accumulation of metabolites, CNS depressant withdrawal Tx
Chlordiazepoxide	Long, may be used to suppress symptoms of withdrawal from CNS depressants
Clorazepate	Long, CNS depressant withdrawal Tx
Diazepam	Long, CNS depressant withdrawal Tx
Temazepam	Intermediate, used for insomnia but can impair driving the next day
Oxazepam	Intermediate
Lorazepam	IV or IM only , intermediate, preanesthetic, emergency for status epilepticus (not for theophylline-induced seizures)
Triazolam	Short, not for anxiety, used for insomnia but can cause anxiety the next day or paranoia *according to exam 3, this can act in the absence of GABA
Midazolam	Short, IM, preanesthetic
Alprazolam	Short, used for depression, agoraphobia, panic disorders, addictive
Clonazepam	Not for anxiety, used for absence seizures,
Flumazenil	BDZ antagonist!
Non-BDZ anxiolytics	
Buspirone	Selective 5HT-1a partial agonist , does NOT promote sleep, takes 1-2wks, anti-depressant, no rebound anxiety upon withdrawal,
Barbiturates	Progressive, dose related CNS depression, ↓ cognitive / motor, leads to sleep without analgesia, can cause severe respiratory depression, rapid tolerance except to respiratory and CV depression, physical dependence, severe withdrawal, can produce hyperalgesia, potentiate GABAergic transmission at low doses, at high doses does not need GABA
Phenobarbital	Powerful induction of microsomal enzymes
Secobarbital	
Thiopental	Short acting, used for anesthesia,

Other	
Ethanol	Metabolized by liver, blood concentration declines linearly with time, disrupts sleep patterns , causes barbiturate like effects, causes ↑ BP, can cause delirium tremens
Methanol	Poisoning, give ethanol
Ethylene glycol	Poisoning, give ethanol
Disulfiram	Used to treat alcoholism by ↑ acetaldehyde
Diphenhydramine	OTC sleep-aid
Hydroxyzine	Can be an anxiolytic or preanesthetic

Opioid analgesics	
Morphine	Activity due to μ receptors , opens K^+ channels, close Ca^{++} channels, inhibit Adenylate cyclase, reduce cAMP, σ receptors responsible for psychotomimetic effects, PCP receptor is open configuration of Ca^{++} channel, has relatively modest affinity for μ receptors, causes analgesia , this is potentiated by TCAs and SSRIs and NSAIDs, without loss of consciousness, specific for pain, continuous is dulled more than sharp, relieves sensory and affective, can also cause respiratory depression by decreasing responsiveness to CO_2 , causes nausea/vomiting, reduces diarrhea (antikinetic), decreases cough, causes hypothermia, may increase ADH release, constricts pupils, excitatory at very high doses, vasodilation, release histamine, no effect on BP, HR, but may produce OHoTN, antikinetic can cause spasm and pain (antagonized by atropine), all routes of admin, conjugated in liver, not accumulated in tissues, 90% ren exc, treat OD with naloxone, tolerance is pharmacodynamic, prominent physical dependence, less severe withdrawal than EtOH, Barbiturates
Heroin	Prodrug converted into morphine (fast), very lipid soluble,
Codeine	Prodrug converted into morphine (slow), Anti-tussive, naloxone-reversible, very effective orally ,
Dextromethorphan	Anti-tussive, not naloxone-reversible, not analgesic, produces CNS depression at high doses, recent abuse
Hydromorphone	Like morphine, more potent
Oxymorphone	Like morphine, more potent
Levorphanol	Better oral, like morphine
Meperidine	All routes, excitatory, can accumulate, naloxone leads to convulsion, less spasmogenic, less constipation and urine retention, does not inhibit cough, used in obstetrical analgesia , less effect on fetus, short action
Diphenoxylate	Used with atropine to treat diarrhea, insoluble, no IV use, no abuse
Fentanyl	80x more potent than morphine, drug of abuse, used with

	droperidol for anesthesia
Methadone	Better availability, lasts longer, is stronger than morphine, produces tolerance and dependence but less withdrawal, used in replacement therapy for opiate addiction
Propoxyphene	Like methadone but less effective than codeine, used for mild to moderate pain, lower abuse than codeine, high toxicity
1-acetylmethadol	Depot, long lasting produces methadone, treat addiction
Pentazosin	Kappa agonist , less abuse pot'l, can induce withdrawal symptoms in pts dependent on morphine, less respiratory depression, less potent, can cause anxiety, disturbing thoughts, nightmares, hallucinations, reduces morphine analgesia, increases BP, HR, NE, Epi
Naloxone/Naltrexone	Antagonists, no effect on normals, produces withdrawal
Gabapentin	Increases release of GABA
Clonidine	May reduce physical craving, withdrawal complications

Chemotherapeutic drugs	
Alkylating Agents:	Most associated with secondary tumors –AML; resistance via decreased drug uptake and increased DNA repair; CCNS; Inhibits DNA synthesis
Mechlorethamine	IV, can cause hyperuricemia (use allopurinol), myelosuppression (blood counts), nausea/vomiting, use in Hodgkin's and other lymphomas
Cyclophosphamide	PO, IV, IM, IP, PRODRUG, most useful in series, can cause hemorrhagic cystitis (give w/ Mesna + fluid), myelosuppression (blood counts), nausea, vesicant, use for leukemia, lymphomas, myeloma, breast CA, soft tissue sarcomas
Ifosfamide	Iv, PRODRUG, hemorrhagic cystitis as above, used in lung and testis CA, lymphomas, soft tissue sarcomas
Thiotepa	IV, causes above problems w/o HC, used for lymphomas, breast CA, malignant melanomas, colon CA, bladder CA (direct)
Carmustine	Nitrosourea- (can cause severe myelodepression, nadir at 6 wks, penetrates CNS), IV
Lomustine	NU, PO, IV
Semustine	NU, PO
Dacarbazine	Monofunctional, IV, inhibits DNA/RNA/protein synthesis, mild myelosuppression, N/V, used for melanoma or in combo for Hodgkin's
Cisplatin	Platinum complexes, IV, no DNA x-linking, resistance is a problem, No myelosuppression , but does have renal toxicity (need hydration and diuresis), ototoxicity, neurotox, used to sensitize to radiation therapy

Carboplatin	Platinum, IV, resistance problem, less SEs than cisplatin, but myelosuppression is worse, used only for ovarian CA
Anti-metabolites:	Interferes with purine synthesis, ultimately DNA synthesis; CCS
Methotrexate	IV, PO, Folic acid analog, binds to DHFR, Resistance via increased DHFR, altered DHFR, decreased influx; I w/ DHFR, decreasing TMP, purine, Met, Ser synthesis, can cause myelosuppression>GI>skin (use LEUCOVORIN), used for ALL, choriocarcinoma, breast CA, head and neck CA, Burkitt's lymphoma
6-mercaptopurine	PO, Purine analog, converted by HGPRT, eventually inhibit DNA/RNA synthesis, R via decreased HGPRT, increased phosphatase, altered PRPP aminotransferase; I w/ DNA/RNA incorporation, can cause myelosuppression, N/V/D, hyperuricemia (give with Xanthine oxidase I or allopurinol), used for AML, ALL
6-thioguanine	PO, Same resistance and action as 6-MP, but no need for XOI, same uses as 6-MP
5-fluorouracil	IV, good CNS penetration, inhibits Thymidylate synthetase, R via decreased uridine kinase, decreased affinity of thymidylate synthetase; I w/ TS, decreased TMP synthesis, inhibits DNA/RNA synthesis, can cause N/D/V, ulcers of oral/GI mucosa, myelosuppression, anorexia, used for adenocarcinomas or topical for skin lesions
Cytarabine	IV, chain termination, S phase specific, DNA polymerase, inhibits DNA synthesis, can cause N/V, Myelosuppression, hepatotoxic, neurotoxic, used for AML, ALL, lymphomas
Antibiotics:	CCNS
Doxorubicin	IV, strand breaks, R via decreased uptake, same action as Daunorubicin (X-resistance with Dactinomycin), can cause mild myelosuppression, cardiac toxicity, alopecia, 'radiation recall', used as a broad spectrum chemo drug- important
Daunorubicin	IV, R via decreased uptake/decreased DR reductase; I w/ RNA synthesis; Topo-II DNA complex, blocks DNA re-ligation, induces oxidants, inhibits DNA synthesis, uses/side effects same as DoxoR
Dactinomycin	IV, inhibits RNA synthesis, R via decreased uptake, DNA intercalation, inhibits DNA/RNA/protein synthesis, 'radiation recall', MS/N/V, alopecia, oral ulcers, dermatitis, used in combo for Wilm's tumor and choriocarcinoma
Mitomycin	Selective based on hypoxic conditions in tumor cells, severe myelosuppression, used in combo for Gut CA, lung CA
Bleomycin	IV, IM, generates reactive oxygen species, DNA scission, I w/ DNA, oxidant formation, causes strand breaks; CCS, can cause minimal myelosuppression , but N/V/F and pulmonary fibrosis, used in combo for testicular tumors

Plant Products: (microtubule inhibitors)	Interferes with protein synthesis; CCS
Vincristine	IV, M phase specific, R via decreased uptake, Tubulin, blocks polymerization into microtubules, prevents mitotic spindle formation, can cause peripheral neuropathy followed by neuritic pain, loss of DTR, ataxia/paralysis, used in ALL, Wilm's, Ewing's Hodgkin's and non-Hodgkin's, rapidly proliferating cancers
Vinblastine	IV, M phase, mitotic spindle, Same resistance as vincristine, can cause myelosuppression, less alopecia, neurotox, stomatitis than VC, used for testicular carcinoma, Hodgkin's, non-Hodgkin's
Paclitaxel	Interferes with mitosis, stabilizes mitotic spindle, but no X-resistance with others, can cause myelosuppression, sensory neuropathy, hypersensitivity, used for melanoma, ovarian, lung and breast CA
Etoposide	Topo-II DNA complex, blocks DNA re-ligation, induces oxidants, inhibits DNA synthesis, some CNS penetration, used for solid tumors, testicular, small cell lung, breast, brain, Kaposi's, Hodgkin's, other lymphomas, AML
Hormones:	R via decreased receptors (uptake)
Tamoxifen	Anti-Estrogen, reduces gene expression, CCNS, one of the least noxious drugs but 3x risk of endometrial CA, used as adjuvant in breast CA surgery and for ER+ tumors
Leuprolide	Agonists at Pit GnRH receptor, reduces testosterone production (hormonal castration), can cause hot flashes, used for metastatic prostate CA that is AR +
Goserelin	See leuprolide
Prednisone	Glucocorticoid receptor, induces gene expression, can cause immunosuppression, used for ALL, Hodgkin's, non-Hodgkin's
Miscellaneous:	
Hydroxyurea	PO, Blocks reduction of ribonucleotides to deoxyribonucleotides, inhibits DNA synthesis, can cause myelosuppression, N/V/D, used for CML, melanoma, head and neck CA
L-asparaginase	IV, Asparagine, reduces extracellular levels, inhibits protein synthesis in tumor cells without ability to synthesize asparagine, can cause hepatotoxicity, antibody response to bacterial protein, used for childhood ALL

APPENDIX 4

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
Home > Faculty							
<input type="checkbox"/>	<input type="checkbox"/>	Lizbeth Hedstrom, Ph.D.					
		Associate Professor of Biochemistry					
		Enzymology					
		Ph.D., Brandeis University					
		contact information (781) 736-2333	Hedstrom Laboratory Web Page Beckman Young Investigators Searle Scholars				
<p>My laboratory is investigating how protein structure determines function with three general aims: 1) to understand the mechanism of enzyme catalysis; 2) to design novel enzymes and 3) to design specific enzyme inhibitors. This work involves a wide array of experimental techniques, including enzyme kinetics, site directed mutagenesis, organic synthesis, protein purification and various methods of monitoring protein structure. We choose problems of pharmacological interest (e.g., IMP dehydrogenase) and paradigms of enzyme action (e.g., trypsin). Our ongoing projects include:</p>							
<table border="1"><tr><td>Mechanism of catalysis and inhibition of IMP dehydrogenase</td><td><input type="checkbox"/></td></tr><tr><td>Rapidly growing cells demand large quantities of nucleotide precursor for DNA</td><td></td></tr></table>				Mechanism of catalysis and inhibition of IMP dehydrogenase	<input type="checkbox"/>	Rapidly growing cells demand large quantities of nucleotide precursor for DNA	
Mechanism of catalysis and inhibition of IMP dehydrogenase	<input type="checkbox"/>						
Rapidly growing cells demand large quantities of nucleotide precursor for DNA							

and RNA synthesis. Inhibition of nucleotide biosynthesis is an important strategy for anticancer, antiviral, immunosuppressive and antimicrobial chemotherapy. IMP dehydrogenase catalyzes the rate-limiting step in guanine nucleotide metabolism, the conversion of IMP to XMP. IMP dehydrogenase inhibitors are used in the treatment of leukemia and kidney transplantation and may prove useful antimicrobial therapy. We are investigating the mechanism of the IMPDH reaction, the mechanism of action of known IMP dehydrogenase inhibitors and designing new inhibitors, with an emphasis toward delineating the differences between human and microbial IMP dehydrogenases.

Trypsin- (a) engineering specificity:

We are investigating the structural basis of substrate specificity in the trypsin family of serine proteases. We have constructed a trypsin mutant with 10% of the activity of chymotrypsin. This feat represents a 10^{10} -fold change in substrate preference. We have also created a protease that cleaves specifically between two Arg residues. Our long term goal is to design a protease with restriction enzyme-like specificity.

(b) understanding zymogen activation: One of the fundamental problems in biochemistry is to understand the forces controlling protein conformation. We are approaching this problem by studying the conformational change which occurs during the biosynthesis of trypsin. This conformational change is essentially an example of protein folding, albeit on a smaller and more confined scale. We are studying the effect of mutations on both the active trypsin conformation and the inactive trypsinogen conformation.

Mechanism of streptokinase action

Streptokinase is a plasminogen activator; it is widely used as a thrombolytic agent to treat heart attacks and stroke. Unlike typical plasminogen activators, streptokinase is not a protease (nor is it a "kinase"). Despite its long history of clinical use, the mechanism of streptokinase action is not understood. We are currently collaborating with Guy Reed at Harvard School of Public Health to investigate mechanism of plasminogen activation by streptokinase. This work should identify streptokinase derivatives with improved chemotherapeutic properties.

Selected Publications:

Huang, Xinyi ; Knoell, Christopher T.; Frey, Gary; Hazegh-Azam, Maryam; Tashjian, Jr., Armen H.; Hedstrom, Lizbeth & Abeles, Robert H. Recombinant human prostate-specific antigen: anion activation and azapeptide inhibitors. Biochemistry, in press.

Pasternak, Annette; White, Andre; Jeffrey, Constance; Medina, Nivia; Cahoon, Marguerite; Ringe, Dagmar & Hedstrom, Lizbeth. The energetic cost of induced fit catalysis: crystal structures of trypsinogen mutants with enhanced activity and inhibitor binding. Protein Science 10, 1331-1342 (2001). [[Abstract](#)]

Sazonova, Irina Y.; Houng, Aiilyan K.; Chowdhry, Shakeel A.; Robinson, Brian R.; Hedstrom, Lizbeth & Reed, Guy L. The mechanism of a bacterial plasminogen activator intermediate between streptokinase and staphylokinase. *J. Biol. Chem.* 276, 12609-12613 (2001). [[Abstract](#)]

McLean, Jeremy E.; Neidhardt, Edie A.; Grossman, Trudy H. & Hedstrom, Lizbeth. Multi-inhibitor analysis of the brequinar and leflunomide binding sites on human dihydroorotate dehydrogenase. *Biochemistry* 40, 2194 -2200 (2001). [[Abstract](#)]

Kerr, Kathleen M.; Digits, Jennifer A.; Kuperwasser, Nicolas & Hedstrom, Lizbeth. "Asp338 Controls Hydride Transfer in *Escherichia coli* IMP Dehydrogenase." *Biochemistry* 39, 9804-9810 (2000). [[Abstract](#)]

Dai, Yong; Hedstrom, Lizbeth & Abeles, Robert H. "Inactivation of Cysteine Proteases by (Acyloxy)methylketones Using S'/P' Interactions." *Biochemistry* 39, 6498-6502 (2000). [[Abstract](#)]

McMillan, Fiona; Cahoon, Marguerite; White, Andre; Hedstrom, Lizbeth; Petsko, Gregory A.; Ringe, Dagmar. "2.4 Å crystal structure of *Borrelia burgdorferi* IMP dehydrogenase: evidence for a substrate induced hinged-lid motion by loop-6." *Biochemistry* 39, 4533-4542 (2000). [[Abstract](#)]

Digits, Jennifer A. & Hedstrom, Lizbeth. "Drug selectivity is determined by coupling across the NAD site of IMP dehydrogenase." *Biochemistry* 39, 1771-1777 (2000). [[Abstract](#)]

Reed, Guy L.; Houng, Aiilyan K.; Liu, Lin; Parhami-Seren, Behnaz; Matsueda, Lee H., Wang, Shunguang and Hedstrom, Lizbeth. "A catalytic switch and the conversion of streptokinase to a fibrin-targeted plasminogen activator." *Proc. Natl. Acad. Sci USA* 96, 8879-8883 (1999). [[Abstract](#)]

Wang, Shunguang; Reed, Guy L. & Hedstrom, Lizbeth. "Deletion of Ile1 of streptokinase impairs plasminogen activation: evidence for the molecular sexuality hypothesis." *Biochemistry* 38, 5232-5240 (1999). [[Abstract](#)]

Pasternak, Annette; Liu, Xiaolin & Hedstrom, Lizbeth. "Activating a zymogen without proteolytic processing: mutation of Lys15 and Asp194 activate trypsinogen." *Biochemistry* 37, 16201-16210 (1998). [[Abstract](#)]

Kurth, Torsten; Grahn, Sibylla; Thormann, Michael; Ullman, Dirk; Hofman, Hans-Jorg; Jakubke, Hans-Dieter and Hedstrom, Lizbeth. "Engineering the S1'-subsite of trypsin: design of a protease which cleaves between dibasic residues." *Biochemistry* 37, 11434-11440 (1998). [[Abstract](#)]

Hung, Su-Hwi & Hedstrom, Lizbeth. "Converting trypsin to elastase: Substitution of the S1 site and adjacent loops reconstitutes esterase specificity but not amidase activity." Protein Engineering, 11, 669-673 (1998). [[Abstract](#)]

Last update: Tuesday, July 24, 2001. E-mail comments or questions to the [webmaster](#).

[Top of Page](#) | [Life Science Faculty](#) | [Home](#)